Journal of
Cardiology & Cardiovascular
Surgery

Original Article

DOI: 10.51271/JCCVS-0011

The relationship between neutrophil to lymphocyte ratio and diastolic dysfunction in patients with essential hypertension

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Cite this article: Doğan Y, Şarlı B. The relationship between neutrophil to lymphocyte ratio and diastolic dysfunction in patients with essential hypertension. *J Cardiol Cardiovasc Surg.* 2023;1(3):36-39.

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Received: 15/08/2023 ◆ **Accepted**: 16/09/2023 ◆ **Published**: 30/09/2023

ABSTRACT

Aim: Diastolic dysfunction (DD), which often accompanies essential hypertension (HT), can progress to heart failure with preserved ejection fraction. Recent studies have shown an association between chronic inflammation and HT. In this study, we aimed to investigate the neutrophil lymphocyte ratio (NLR) in hypertensive patients with and without DD and the relationship between NLR and DD development.

Methods: The study included 50 patients with DD and 50 patients without DD. Left ventricular systolic and diastolic functions were evaluated by echocardiography in all patients. A complete blood count, C-reactive protein (CRP), and NLR were analyzed in blood samples obtained from the patients.

Results: There was no significant difference in demographic characteristics and biochemical values between the two groups. White blood cell count and NLR were significantly higher in the group with DD ($p<0.001$). There was a strong correlation between the presence of DD and NLR in hypertensive patients ($r=0.814$, $p<0.001$). Although CRP was between reference values in both groups, it was significantly higher in the group with DD compared to the group without DD (4.40±1.60 vs. 3.70±0.90, $p=0.020$).

Conclusion: NLR can be used to detect DD in patients with hypertension and is an easily accessible and inexpensive inflammatory marker.

Keywords: Hypertension, diastolic dysfunction, neutrophil/lymphocyte ratio.

INTRODUCTION

In 2/3 of patients with congestive heart failure (CHF), the clinical picture is a combination of systolic and diastolic dysfunction (DD), whereas left ventricular (LV) function is preserved in the remaining 1/3.[1] This clinical condition, which is thought to be due to DD, is not significantly different from systolic HF in terms of mortality, which further emphasizes the importance of detecting DD.[2] Essential hypertension (HT) is the most common comorbidity in patients with diastolic HF.[3] In patients with HT, the first cardiac change detected is LV DD, with or without left ventricular hypertrophy (LVH).

NLR, an inflammation parameter that has almost routinely begun to be included in laboratory results along with hemogram parameters, has been shown in many studies to have an important role in determining the severity and prognosis of many cardiovascular diseases, including HT.[4-14] Inflammatory mediators play an important role in myocardial contractility, remodeling, and endothelial dysfunction and have been shown to be associated with symptom onset and mortality.[15,16] However, studies showing the relationship between LV diastolic function and NLR are limited. In this study, we investigated the relationship between NLR and LV DD in patients with HT.

METHODS

Study Subjects

The study included a total of 100 patients admitted to the cardiology outpatient clinic between June and September 2013 with a diagnosis of HT. Fifty participants with grade I LV DD detected by echocardiography were accepted as the patient group. Fifty HT patients without LV DD were considered the control group. All patients were between 30 and 70 years of age, were on antihypertensive medication, and had normal electrocardiograms (ECG). Exclusion criteria were type II diabetes mellitus, coronary artery disease, other cardiac diseases (valvular heart disease, cardiomyopathy, HF, etc.), renal failure, recent cerebrovascular disease, and a history of alcohol and smoking. A physical examination,

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outpatient blood pressure measurement, detailed background and habit questioning, and 12-lead ECG were performed in all patients.

Blood Pressure Measurement

After the patients had rested for at least 10 minutes, their blood pressures were measured in the supine position in both arms with a mercury sphygmomanometer with a suitable cuff by the same person based on Korotkoff phase I and phase V sounds. The blood pressures of subjects with elevated blood pressure were measured again 10 minutes later.

Laboratory Assessments

Biochemical measurements were analyzed in blood samples obtained after at least 12-14 hours of fasting. Fasting blood glucose, urea, creatinine, total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL) cholesterol, and triglyceride levels were measured in all patients. LDL Cholesterol: Calculated by the formula TK- [(TG/5) + HDL]. For an automated complete blood count, samples were collected from the antecubital vein in vacuum tubes containing EDTA (15% K3 EDTA 0.054 ml / 4.5 ml blood), and the samples were analyzed within 1 hour (Mindray BC 6800).

Echocardiographic Evaluation

With the patients in the left lateral decubitus position, echocardiographic measurements were performed by the same person in accordance with the recommendations of the American Society of Echocardiography using two-dimensional, M Mode, C-Doppler, and tissue Doppler with parasternal long axis, short axis, apical four-space, and five-space views. All echocardiograms were performed transthoracically with a Philips HD 11 xe Echo device. In accordance with the recommendations of the American Society of Echocardiography, all echocardiograms were performed by the same person and at midday to eliminate the effect of circadian changes on diastolic function. The intermittent Doppler sample was placed parallel to the flow (<20°) at the mitral valve cusps in the apical four-cavity view, and the mitral flow trace was obtained to obtain early mitral peak flow velocity (E), late mitral flow velocity (A), E/A ratio, and deceleration time (DT) of the E wave. To measure the deceleration time, the time between the peak of the E flow velocity and the point at which it decreased to the baseline was measured. The E/A ratio was calculated by finding the highest values of mitral valve E and A flow velocities. For isovolumetric relaxation time (IVRT) measurement, the transducer was directed towards the left ventricular outflow tract after placing the sample volume over the mitral valve cusps. When aortic Doppler flow was seen, the IVRT was found by measuring between the point where aortic flow ended and mitral flow began. In the apical four-cavity image, a 5-mm tissue Doppler sample volume was placed on the septal and lateral edges of the mitral annulus, and measurements were made. Ejection fraction, pulmonary venous systolic wave velocity/pulmonary venous diastolic wave velocity (PVs/PVd) were also measured with the Biplane Simpson model.

Statistics

The data obtained in the study were recorded in SPSS (Statistical Package for Social Sciences) version 18.0. The Kolmogorov-Simirnov test was used to determine that the distributions of the variables were normal. Normal distributions of continuous variables are presented as mean values and standard deviations. The statistical analysis of parametric variables between the two groups was performed using the student t test. Mann Whitney The U test was used for nonparametric variables. Qualitative variables were presented as percentages, and the correlation of variables was performed using the Chi-Square test. The relationship between variables was also evaluated by Pearson and Spearman correlation analyses. A probability coefficient of $p<0.05$ was considered statistically significant.

RESULTS

Of the 100 patients included in the study, 47 had stage I HT and 53 had stage II HT. There was no difference between the groups in terms of the HT stage distribution. There was no significant difference in baseline demographic findings between the two groups. There was also no significant difference between the two groups in terms of renal function tests, blood glucose, and lipid panels. E/A ratio, DT (ms), IVRT, and PVs/PVd ratio were significantly different in the echocardiography findings of the group with DD compared to the group without DD. White blood cell count and NLR were significantly higher in the group with DD ($p<0.001$). There was a strong correlation between the presence of DD and NLR in patients with HT ($r=0.814$, $p<0.001$). CRP was significantly higher in the group with DD compared to the group without DD ($p=0.020$) (**Table I, II**).

Table 1. Demographic and laboratory characteristics of the patients

	Group with diastolic dysfunction n=50	Group with nondiastolic dysfunction n=50	p
Age (year)	54.5± 7.7	52.6± 8.2	0.228
Gender (Male)	19	22	0.456
Glucose (mg/dL)	98.9± 15.3	97.3± 12.9	0.570
BUN(mg/dL)	15.4±4.1	14.4±4.3	0.241
Kreatinin (mg/dL)	0.7±0.2	0.7±0.1	0.956
LDL cholesterol(mg/dL)	113.3±32.2	104.2±29.	0.145
Total cholesterol(mg/dL)	190.6±39.1	186.3±35.8	0.566
Triglyceride (mg/dL)	157±56.1	159±55.2	0.862
HDL cholesterol(mg/dL)	45.6±13.1	47.5±10.2	0.418
WBC (10^3/mm^3)	8.8±1.6	7.6±1.7	<0.001
N/L ratio	6.1±2.7	1.6±0.7	<0.001
CRP mg/dL	4.4±1.6	3.7±0.9	0.020

(BUN: blood urea nitrogen, LDL: low-density lipoprotein, HDL: high-density lipoprotein,WBC: White blood cell, CRP: C-reaktif protein, N/L: neutrophil to lymphocyte ratio)

Table 2. Echocardiographic findings of the patients

	Group with diastolic dysfunction n=50	Group with nondiastolic dysfunction n=50	p
EF (%)	62.9± 3.1	65.8± 4.7	0.121
E/A	0.61±0.24	0.94±0.32	<0.05
DT (ms)	202±34	185±24	<0.05
IVRT (ms)	95±12	87±8	<0.05
(PVs/PVd)	0.96±0.31	0.71±0.21	<0.05
S' septum(cm/s)	6.8±1.1	7.3±1.21	0.066
E' septum (cm/s)	8.2±2.3	11.1±2.4	<0.05
E/E' septum	9.6±2.1	8.6±2.4	0.122
S' lateral (cm/s)	7.7±1.8	9.2±2	<0.05
E'lateral (cm/s)	9.6±2.3	13.1±2.8	<0.05
E/E' lateral	8.4±2.1	6.7±1.8	<0.05

(EF: ejection fraction, DT: deceleration time, IVRT: isovolumetric relaxation time, PVs/PVd: Pulmonary venous systolic wave velocity/pulmonary venous diastole wave velocity)

DISCUSSION

In our study, we found that white blood cells and NLR were significantly higher in the group with diastolic dysfunction. Considering that DD may progress to diastolic HF over time, this finding suggests that NLR may be used to predict the development of HF. In recent years, an association between HT and the presence of low-grade chronic inflammation has been demonstrated.[17] It is not known whether inflammation is a cause or a consequence of HT. Endothelial dysfunction may lead to HT, and HT itself may negatively affect endothelial function.[18,19] The vascular adventitia layer, which was previously considered only as a physical barrier, is now known to be an important source of free oxygen radicals that play an important role in the pathophysiology of HT. Collagen deposition in the interstitial space due to the inflammatory process leads to cardiac fibrosis. Cardiac fibrosis results in myocardial stiffness and DD.[20,21] Studies have found a correlation between low-grade systemic inflammation and high arterial stiffness and, progressively, ventricular stiffness and diastolic failure.[22,23] Dorfells et al.[24] proved that hypertensive patients have increased the release of IL-1 and TNF-α from peripheral blood monocytes compared to non-hypertensive patients. CRP, an inflammatory marker, has been shown to be higher in patients with essential HT compared to healthy subjects. In addition, some recently published studies have shown the presence of higher CRP levels in patients in the pre-HT stage compared to normotensive individuals.[25,26] Vasan et al. [27] showed that the inflammatory pathway is a very strong factor in cardiac remodeling and that systemic inflammatory markers (CRP, IL-6, TNF-α) are strong independent risk factors for HF. Masiha et al. [28] found a significant association between inflammatory markers and LVH in hypertensive patients. Inflammatory mediators were found to be higher in hypertensive patients with LVH compared to hypertensive patients without LVH.[29] In our study, CRP levels were found to be higher in patients with LVH due to HT, in accordance with the literature; therefore, it can be concluded that inflammation levels were higher. In recent years, NLR has been studied in all cardiovascular diseases, and the relationship between NLR and cardiovascular diseases has been shown. In parallel with this, it has been demonstrated that it is an independent marker of prognosis in HF, stable angina pectoris, and acute coronary syndromes.[8,11,30] In a study by Imtiaz et al.[31], NLR was found to be higher in hypertensive patients than in normal subjects. In a study by Demir et al.[32], NLR was found to be significantly higher in patients with non-dipper HT than in patients with dipper HT. It has been shown that there is a positive correlation between NLR and elevated blood pressure.[32]

In patients with hypertension, the autonomic nervous system can activate neutrophils, which can cause vascular system damage, penetrate the arteries, heart and kidney, drive fibrosis by secreting oxidants and proinflammatory molecules, and promote the recruitment of other immune cells for tissue inflammation.[33] The presence of these markers in individuals with normal blood pressure is associated with an increased risk of hypertension, whereas in patients with essential hypertension, levels of these markers are associated with target organ damage and may help predict the risk of cardiovascular events.[34] Many studies have investigated the effects of these inflammatory markers. Chronic inflammation can also trigger oxidative stress, which has been shown to be associated with hypertension and its consequences. This cycle of pathology contributes to the adverse outcomes of HTN patients.[35,36]

In our study, NLR was significantly higher in patients with diastolic dysfunction than in patients without DD. There was also a strong positive correlation between NLR and the presence of diastolic dysfunction. Possible pathophysiologic mechanisms that may explain this relationship are: inflammation, which is accepted as both a cause and a consequence of hypertension, may cause cardiac fibrosis, impair left ventricular compliance, and lead to the development of DD; and the inflammatory environment may contribute to the development of clinical/subclinical CAD and lead to the development of DD.[5,30] In our study, the high NLR in hypertensive patients with DD suggests that chronic inflammation plays a role in the development of DD.

Study Limitations

This study was conducted with a relatively small sample, and it may not be accurate in predicting its results for all HT patients. To confirm the results of this single-center study, a larger multicenter study with larger participation would be more appropriate. LV DD was determined only by some echocardiographic measurements and was not checked invasively, which may have led to some inaccurate results. Although patients with coronary artery disease were excluded, they may not have been fully excluded because coronary angiography and/or noninvasive ischemia were not investigated.

CONCLUSION

In conclusion, CRP, an inflammatory marker whose importance is well known in identifying high-risk patient groups in terms of cardiovascular disease, and NLR levels were found to be significantly associated with DD. NLR can be used as a biochemical marker to determine the presence of DD and predict the progression to HF in patients with HT.

ETHICAL DECLARATIONS

Ethic Committee Approval: The approval of the ethics committee, Kayseri Training and Research Hospital, dated 11.07.2013 and numbered 52332816/13084 was obtained

before the study, and it was conducted in accordance with the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained from the patients before the study.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare. Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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